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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,641	11/15/2001	Avi J. Ashkenazi	P2730P1C39	7553

35489 7590 06/30/2004

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,641	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-124 and 127-131* is/are rejected.

7)☐ Claim(s) *125 and 126* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendments filed 11/15/2001 and 9/30/2002 have been entered in full.

2. Claims 1-118 are cancelled.

3. Claims 119-131 have been added.

4. Claims 119-131 are pending and under examination.

Specification

5. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 307, line 28 and page 310, line 13. Applicant is required to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 119-124, 128 and 130-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 119-124, 128 and 130-131 are indefinite in the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 119, part (d), for example) as a signal sequence is not generally considered to be part of an extracellular domain. Further, because the "extracellular domain" is not defined in the specification or in Figure 278, it is unclear what the extracellular domain actually is.

b. Claim 131 is indefinite for reciting "epitope tag" because the exact meaning of the phrase is not clear. Does the phrase mean an "epitope" where and antibody binds or a tag that allows for purification that is an amino acid sequence that does not require binding to an antibody, or some other tag?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 119-123, and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80% amino acid sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the sequence set forth in SEQ ID NO:387 (i.e., PRO1312), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 119-124 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession no. 203132. It is not clear whether the cDNA deposited as ATCC accession no. 203132 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:386 or encodes SEQ ID NO:387 or contains additional sequences in addition to SEQ ID NO:386.

Applicant's referral to the deposit of the cDNA on pages 563-566 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant

of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to

corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

11. Claims 119-123 and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:387 (i.e., PRO1312) or the extracellular domain thereof. There is no functional limitation in the claims as far as to

the polypeptide. Applicants have taught the polypeptide consisting of the extracellular domain or, more accurately, the mature form of PRO1312, as well as the putative signal sequence (approximately amino acids 1-14 of PRO1312, see page 502, lines 27-29). The specification discloses the polypeptide was positive for chondrocyte re-differentiation (Assay 110; see page 530) as well as the chondrocyte proliferation assay (Assay 111; see page 531). The specification does not teach an activity for the polypeptide or any active regions of the polypeptide. Thus, one would not know if the polypeptide with the claimed homology would function as a polypeptide of PRO1312.

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. Since PRO1312 is a transmembrane protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory signal. The functional domain of the protein is the mature form. Knowledge of the structure and function of PRO1312 does not provide predictability about function of a structurally related protein, even within the same class.

There are no working examples of polypeptides less than 100% identical to the PRO1312 polypeptide or the mature form thereof. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. Even if the claimed polypeptides had a function. the specification does not provide guidance for using polypeptides related to (*i.e.*, 80%-99% identity) but not identical to PRO1312. The claims are broad because they do not require the claimed

polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

It is well known in the art that even a single modification or substitution in a protein sequence can alter the proteins function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Priority

12. The examiner acknowledges the priority statement filed 9/3/2002, however, priority documents PCT/US99/28313, 09/380,137, PCT/US99/12252 and 60/096,960 do not support a specific and substantial asserted utility or a well-established utility because these applications do not disclose the chondrocyte re-differentiation assay (Assay 110) or the chondrocyte proliferation assay (Assay 111). Therefore, for purposes of applying prior art, the instant claims are granted the priority date of PCT/US00/08439, 3/30/2000.

Claim Rejections

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 119-122 and 130-131 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al (WO 99/58660, 11/18/1999).

The claims recite isolated polypeptides having at least 80% amino acid identity with the polypeptide of SEQ ID NO:387 (i.e., PRO1312) or the extracellular domain thereof, lacking its associated signal peptide or the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession no. 203132, a chimeric polypeptide comprising an epitope tag or an Fc region of an immunoglobulin.

Ruben et al teach a polypeptide sequence (SEQ ID NO:122; pages 73-74 of sequence listing) having at least 97% amino acid identity with residues 1-206 of the polypeptide of SEQ ID NO:387 (see the alignment attached to the back of this Office Action; Result 214). Ruben et al teach chimeric polypeptides wherein the polypeptide is fused to the Fc region of an immunoglobulin or to an "HA" tag, corresponding to an epitope derived from the influenza hemagglutinin protein (i.e., an epitope tag) (see pages 197-198, particularly page 198, lines 6-8 and 23-24).

15. Claim 119 is rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al (Kidney International, 56(2):549-558, August 1999).

The claim has been described supra.

Zhang et al teach a polypeptide having at least 80% amino acid identity with residues 1-206 of the polypeptide of SEQ ID NO:387 (see the alignment attached to the back of this Office Action; Result 2).

16. Claims 119-122 and 130-131 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobs et al (WO 98/32853, 7/30/1998).

The claims have been described supra.

Jacobs et al teach a polypeptide (SEQ ID NO:4, pages 65-66) having at least 97% amino acid identity with residues 1-206 of the polypeptide of SEQ ID NO:387 (see the alignment attached to the back of this Office Action; Result 212). Jacobs et al teach chimeric polypeptides having an epitope tag (see page 36, lines 4-6).

17. Claims 119-122 are rejected under 35 U.S.C. 102(b) as being anticipated by Edwards et al (WO 99/06439, 2/11/1999).

The claims have been described supra.

Edwards et al teach a polypeptide (SEQ ID NO:27, pages 17-18 of sequence listing) having at least 95% amino acid identity with residues 1-206 of the polypeptide of SEQ ID NO:387 (see the alignment attached to the back of this Office Action; Result 215).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 119 and 130-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Kidney International, 56(2):549-558, August 1999). in view of Grose (U.S. Patent 5,710,248, issued 1/20/98).

Claims 119 and 130-131 have been described supra.

Zhang et al have been described supra. Zhang et al does not teach a chimeric protein comprising an epitope tag. This deficiency is made up for in the teachings of Grose.

Grose teach a peptide tag for immunopurification and immunodetection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric polypeptide comprising SEQ ID NO:387 and a peptide tag.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric polypeptide comprising SEQ ID NO:387 and a peptide tag because Grose teach insertion of a peptide tag into a protein facilitates the characterization of the protein when antibodies to the protein are not available (see column 1, lines 10-12). Thus, it would have been obvious to one of ordinary skill in the art to have added a peptide tag to the polypeptide of SEQ ID NO;387 for purification.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. Claims 119-122 and 130-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (WO 99/06439, 2/11/1999) in view of Grose (U.S. Patent 5,710,248, issued 1/20/98).

The claims have been described supra.

Edwards et al have been described supra. Edwards et al does not teach a chimeric protein comprising an epitope tag. This deficiency is made up for in the teachings of Grose.

Grose teach a peptide tag for immunopurification and immunodetection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric polypeptide comprising SEQ ID NO:387 and a peptide tag.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric polypeptide comprising SEQ ID NO:387 and a peptide tag because Grose teach insertion of a peptide tag into a protein facilitates the characterization of the protein when antibodies to the protein are not available (see column 1, lines 10-12). Thus, it would have been obvious to one of ordinary skill in the art to have added a peptide tag to the polypeptide of SEQ ID NO;387 for purification.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

21. No claim is allowed.

22. Claims 125-126 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all relevant limitations of the base claim and any intervening claims.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER